

THE CLAIMS

What is claimed is:

- 5 1. A method of treating or preventing a disorder that is ameliorated by the inhibition of neuronal monoamine reuptake which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a bupropion metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.
- 10 2. The method of claim 1 wherein the bupropion metabolite is optically pure.
3. The method of claim 2 wherein the optically pure bupropion metabolite is (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (R,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone; or (S)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone.
- 15 4. The method of claim 3 wherein the optically pure bupropion metabolite is optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol.
- 20 5. The method of claim 1 wherein adverse effects associated with the administration of racemic bupropion are reduced or avoided.
- 25 6. The method of claim 1 wherein the bupropion metabolite, or pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is adjunctively administered with a second pharmacologically active compound.
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7. The method of claim 6 wherein the second pharmacologically active compound is selected from the group consisting of selective serotonin reuptake inhibitors, 5-HT₃ inhibitors, and nicotine.

5 8. A method of treating or preventing sexual dysfunction which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a bupropion metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

10 9. The method of claim 8 wherein the patient is male.

10. The method of claim 9 wherein the sexual dysfunction is erectile dysfunction.

15 11. The method of claim 8 wherein the patient is female.

12. The method of claim 8 wherein the bupropion metabolite is optically pure.

13. The method of claim 8 wherein the optically pure bupropion metabolite is
20 (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (R,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-
25 propanone; and (S)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone.

14. The method of claim 13 wherein the optically pure bupropion metabolite is optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol.

30 15. The method of claim 8 wherein the bupropion metabolite, or pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is administered orally, transdermally, or mucosally.

16. The method of claim 8 wherein the bupropion metabolite, or pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is adjunctively administered with a 5-HT₃ antagonist.

5 17. The method of claim 16 wherein the 5-HT₃ antagonist is an antiemetic agent.

18. The method of claim 17 wherein the 5-HT₃ antagonist is selected from the group consisting of granisetron, metoclopramide, ondansetron, renzapride, zacopride, norcisapride, tropisetron, and optically pure stereoisomers, active metabolites, and
10 pharmaceutically acceptable salts, hydrates, solvates, hydrates, and clathrates thereof.

19. A method of treating or preventing an affective disorder which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a bupropion metabolite, or a pharmaceutically
15 acceptable salt, solvate, hydrate, or clathrate thereof.

20. The method of claim 19 wherein the bupropion metabolite is optically pure.

21. The method of claim 20 wherein the optically pure bupropion metabolite is
20 (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (R,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-
25 propanone; or (S)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone.

22. The method of claim 21 wherein the optically pure bupropion metabolite is optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morphinol.

30 23. The method of claim 19 wherein adverse effects associated with the administration of racemic bupropion are reduced or avoided.

24. The method of claim 19 wherein the bupropion metabolite, or pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is adjunctively administered with a therapeutically or prophylactically effective amount of a second pharmacologically active compound.

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25. The method of claim 24 wherein the second pharmacologically active compound is selected from the group consisting of selective serotonin reuptake inhibitors, 5-HT₃ inhibitors, and nicotine.

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26. The method of claim 19 wherein the affective disorder is depression.

27. The method of claim 19 wherein the affective disorder is narcolepsy.

28. The method of claim 19 wherein the affective disorder is nicotine addiction.

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29. A method of treating or preventing a cerebral function disorder which comprises administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a bupropion metabolite or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

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30. The method of claim 29 wherein the bupropion metabolite is optically pure.

31. The method of claim 29 wherein the optically pure bupropion metabolite is (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (R,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone; or (S)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone.

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32. The method of claim 31 wherein the optically pure bupropion metabolite is optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol.

33. The method of claim 29 wherein the bupropion metabolite, or pharmaceutically acceptable salt, solvate, or clathrate thereof, is administered orally, transdermally, or mucosally.

5 34. The method of claim 29 wherein the bupropion metabolite, or pharmaceutically acceptable salt, solvate, hydrate or clathrate thereof is adjunctively administered with a therapeutically or prophylactically effective amount of a second pharmacologically active compound.

10 35. The method of claim 29 wherein the cerebral function disorder is Parkinson's disease.

36. The method of claim 29 wherein the cerebral function disorder is epilepsy.

15 37. The method of claim 29 wherein the cerebral function disorder is Alzheimer's disease.

38. The method of claim 29 wherein the cerebral function disorder is dementia.

20 39. A method of eliciting smoking cessation which comprises administering to a patient in need thereof a therapeutically effective amount of a bupropion metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof.

40. The method of claim 39 wherein the bupropion metabolite is optically pure.

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41. The method of claim 39 wherein the optically pure bupropion metabolite is (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (R,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone; or (S)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone.

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42. The method of claim 41 wherein the optically pure bupropion metabolite is optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol.

43. The method of claim 39 wherein the bupropion metabolite, or
5 pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is administered orally, mucosally, or transdermally.

44. The method of claim 43 wherein the bupropion metabolite, or
pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is administered
10 transdermally.

45. The method of claim 39 wherein the bupropion metabolite, or
pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is adjunctively
administered with a therapeutically effective amount of nicotine or a muscarinic receptor
15 antagonist.

46. The method of claim 39 wherein the bupropion metabolite, or
pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is adjunctively
administered with a therapeutically effective amount of nicotine.
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47. The method of claim 46 wherein the nicotine and/or bupropion metabolite or
pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is administered
orally, mucosally, or transdermally.

48. The method of claim 46 wherein the nicotine and/or bupropion metabolite,
25 or pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, is administered transdermally.

49. A method of treating or preventing incontinence which comprises
30 administering to a patient in need of such treatment or prevention a therapeutically or prophylactically effective amount of a bupropion metabolite, or a pharmaceutically acceptable salt, solvate, hydrate or clathrate thereof.

50. The method of claim 49 wherein the bupropion metabolite is optically pure.

51. The method of claim 49 wherein the optically pure bupropion metabolite is (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (R,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone; and (S)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone.

52. The method of claim 51 wherein the optically pure bupropion metabolite is optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol.

53. The method of claim 49 wherein the incontinence is urinary incontinence.

54. The method of claim 53 wherein the urinary incontinence is stress urinary incontinence

55. The method of claim 49 wherein the patient is a human of an age greater than about 50 years or less than about 13 years.

56. A pharmaceutical composition which comprises a bupropion metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, and a pharmaceutically acceptable diluent, carrier, or excipient.

57. The pharmaceutical composition of claim 56 wherein the bupropion metabolite is optically pure.

58. The method of claim 56 wherein the optically pure bupropion metabolite is (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (R,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone; or (S)-1-(3-chlorophenyl)-2-[(1,1-dimethylethanol)amino]-1-propanone.

59. The pharmaceutical composition of claim 58 wherein the optically pure bupropion metabolite is optically pure (S,S)-hydroxybupropion.

60. The pharmaceutical composition of claim 56 wherein said pharmaceutical composition further comprises a second pharmacologically active compound selected from the group consisting of selective serotonin reuptake inhibitors, 5-HT₃ inhibitors, and nicotine.

61. A pharmaceutical unit dosage form comprising a bupropion metabolite, or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

62. The pharmaceutical unit dosage form of claim 61 wherein said dosage form is stored in a sterile container.

63. The pharmaceutical unit dosage form of claim 61 wherein said dosage form is solid.

64. The pharmaceutical unit dosage form of claim 61 wherein said dosage form is a sterile solution or dispersion.

65. The pharmaceutical unit dosage form of claim 61 wherein said dosage form is a transdermal patch.

66. The pharmaceutical unit dosage form of claim 61 wherein the bupropion metabolite is optically pure.

67. The pharmaceutical unit dosage form of claim 62 wherein the optically pure
5 bupropion metabolite is (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol;
(S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; (R,R)-2-(*tert*-
butylamino)-1-(3-chlorophenyl)-propan-1-ol; (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-
propan-1-ol; (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R,S)-2-(*tert*-
butylamino)-1-(3-chlorophenyl)-propan-1-ol; (R)-1-(3-chlorophenyl)-2-[(1,1-
10 dimethylethanol)amino]-1-propanone; or (S)-1-(3-chlorophenyl)-2-[(1,1-
dimethylethanol)amino]-1-propanone.

68. The pharmaceutical unit dosage form of claim 67 wherein the optically pure
15 bupropion metabolite is optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-
morpholinol.

69. The pharmaceutical unit dosage form of claim 61 wherein said dosage form
further comprises a second pharmacologically active compound selected from the group
consisting of selective serotonin reuptake inhibitors, 5-HT₃ inhibitors, and nicotine.

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70. The pharmaceutical unit dosage form of claim 61 wherein said dosage form
is suitable for oral, mucosal, or transdermal administration to a patient.

71. A pharmaceutical unit dosage form suitable for transdermal administration to
25 a patient which comprises nicotine and a bupropion metabolite or pharmaceutically
acceptable salt, solvate, hydrate, or clathrate thereof.

72. A lactose-free solid pharmaceutical unit dosage form comprising an a
bupropion metabolite or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate
30 thereof and a non-lactose carrier, diluent, or excipient.

73. The lactose-free solid pharmaceutical unit dosage form of claim 72 wherein the bupropion metabolite is optically pure.

74. The pharmaceutical unit dosage form of claim 72 wherein said dosage form
5 is an oral dosage form.

75. A process for preparing optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises:

10 brominating 2-chloropropiophenone to form an intermediate;

contacting the intermediate with 2-amino-2-methyl-1-propanol under suitable reaction conditions for the formation of racemic 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol;

15 contacting the racemic 2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol with a chiral acid under suitable reaction conditions to form a mixture of diastereomeric salts;

isolating from the mixture of the diastereomeric salts a chiral salt of (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol; and

20 contacting the chiral salt of (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol with a base.

76. The process of claim 75 wherein the formation of diastereomeric salts and/or isolation of the chiral salt of (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol gives a mother liquor.

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77. The process of claim 75 wherein said mother liquor is contacted with a second chiral acid to form a second mixture of diastereomeric salts, from which the chiral salt of (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol is isolated.

30 78. The process of claim 77, wherein the chiral acid is selected from the group consisting of optically pure derivatives of camphor, tartaric acid, malic acid, and mandelic acid.

79. The process of claim 75, wherein the base is selected from the group consisting of potassium carbonate, potassium hydroxide, sodium hydroxide, and ammonium hydroxide.

5 80. The process of claim 75, wherein the chiral acid is di-*p*-toluoyl-*L*-tartaric acid.

81. A process for preparing racemic erythro-dihydrobupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises:
10 reducing racemic bupropion with a suitable reducing agent to form a racemic erythro/threo dihydrobupropion mixture; and
isolating racemic erythro-dihydrobupropion from the mixture.

82. The process of claim 81 wherein the reducing agent is a metal hydride.
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83. The process of claim 81 wherein the metal hydride is Red-Al.

84. The process of claim 81 wherein the acid is hydrobromic acid, hydroiodic acid, or hydrochloric acid.
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85. The process of claim 84 wherein the acid is hydrochloric acid.

86. A process for preparing optically pure erythro (R,S)-dihydrobupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises:
25 contacting 3-chloropropiophenone with a silyl chloride under reaction conditions suitable for the formation of Z-1-(3-chlorophenyl-1-silyloxy)-1-propene intermediate;
asymmetrically dihydroxylating the intermediate under reaction conditions suitable for the formation of a 2-(S)-hydroxy intermediate;
30 converting the hydroxyl group of the 2-(S)-hydroxy intermediate to a leaving group and reacting with *t*-butyl amine; and
reducing the ketone.

87. The process of claim 86 wherein the base is selected from the group consisting of lithium diisopropylamide (LDA) and lithium hexamethyl disilylamide (LiHMDS).

5 88. The process of claim 86 wherein the silyl chloride is selected from the group consisting of trimethyl silyl chloride and tributyl silyl chloride.

89. The process of claim 86 wherein the silyl chloride is tert-butyldimethylsilyl chloride.

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90. The process of claim 86 wherein the leaving group is a tosylate, mesylate, or nosylate or a triflate.

91. The process of claim 90 wherein the leaving group is a triflate.

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92. The process of claim 86 wherein the reducing agent is a metal hydride.

93. The process of claim 86 wherein the reducing agent is Red-Al.

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94. A process for preparing optically pure erythro (S,R)-dihydrobupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises:

contacting 3-chloropropiophenone with a silyl halide under reaction conditions suitable for the formation of a Z-1-(3-chlorophenyl-1-silyloxy)-1-propene intermediate;

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asymmetrically dihydroxylating the intermediate under reaction conditions suitable for the formation of a 2-(R)-hydroxy intermediate;

converting the hydroxyl group of the 2-(R)-hydroxy intermediate to a leaving group and reacting with t-butyl amine; and

reducing the ketone.

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95. The process of claim 94 wherein the base is selected from the group consisting of lithium diisopropylamide (LDA) and lithium hexamethyl disilylamide (LiHMDS).

5 96. The process of claim 94 wherein the silyl halide is selected from the group consisting of trimethyl silyl chloride, tributyl silyl chloride, and tert-butyldimethylsilyl chloride.

10 97. The process of claim 94 wherein the leaving group is a tosylate, mesylate, or nosylate or a triflate.

98. The process of claim 94 wherein the leaving group is a triflate.

15 99. The process of claim 94 wherein the reducing agent is a metal hydride.

100. The process of claim 94 wherein the reducing agent is Red-Al.

20 101. A process for preparing racemic-threo dihydrobupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises:
reducing racemic bupropion to provide an product; and
purifying the product.

102. The process of claim 101 wherein the reducing agent is a metal hydride.

25 103. The process of claim 101 wherein the reducing agent is borane-tetrahydrofuran.

30 104. A process for synthesizing racemic erythro-dihydro hydroxybupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises
reducing racemic hydroxybupropion with a reducing agent; and
purifying racemic erythro-dihydro hydroxybupropion.

105. The process of claim 104 wherein the reducing agent is a metal hydride.

106. The process of claim 104 wherein the purification is chromatography, filtration, or crystallization.

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107. A process for synthesizing optically pure erythro (R,S)-dihydro hydroxybupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises

reducing (S,S)-hydroxybupropion with a reducing agent; and
10 purifying to give optically pure erythro (R,S)-dihydro hydroxybupropion.

108. The process of claim 107 wherein the reducing agent is a metal hydride.

109. The process of claim 107 wherein the purification is chromatography,
15 filtration, or crystallization.

110. A process for synthesizing optically pure erythro (S,R)-dihydro hydroxybupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises

20 reducing (R,R)-hydroxybupropion with a reducing agent; and
purifying to give optically pure erythro (S,R)-dihydro hydroxybupropion.

111. The process of claim 110 wherein the reducing agent is a metal hydride.

112. The process of claim 110 wherein the purification is chromatography,
25 filtration, or crystallization.

113. A process for synthesizing optically pure threo (S,S)-dihydro hydroxybupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate
30 thereof which comprises

reducing (S,S)-hydroxybupropion with a reducing agent; and
purifying to give optically pure threo (S,S)-dihydro hydroxybupropion.

114. The process of claim 113 wherein the reducing agent is a metal hydride.

115. The process of claim 113 wherein the purification is chromatography, filtration, or crystallization.

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116. A process for synthesizing optically pure threo (R,R)-dihydro hydroxybupropion or a pharmaceutically acceptable salt, solvate, hydrate, or clathrate thereof which comprises

reducing (R,R)-hydroxybupropion with a reducing agent; and
10 purifying to give optically pure threo (R,R)-dihydro hydroxybupropion.

117. The process of claim 116 wherein the reducing agent is a metal hydride.

118. The process of claim 116 wherein the purification is chromatography,
15 filtration, or crystallization.

119. Optically pure (R,R)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol hydrochloride.

20 120. Optically pure (S,S)-2-(3-chlorophenyl)-2-hydroxy-3,5,5-trimethyl-morpholinol hydrochloride.

121. Optically pure (R,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol hydrochloride.

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122. Optically pure (S,R)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol hydrochloride.

123. Optically pure (S,S)-2-(*tert*-butylamino)-1-(3-chlorophenyl)-propan-1-ol
30 hydrochloride.

